UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DN

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/484,537	06/07/95	QUEEN C	11823-002630

020350 HM12/0429

TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER EIGHTH FLOOR
SAN FRANCISCO CA 94111

EXAMINER	
BURKE, J	
ART UNIT	**PAPER NUMBER**
1642	28

DATE MAILED: 04/29/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/484,537	Applicant(s) Queen et al
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1642

☒ Responsive to communication(s) filed on *5/14/98; 8/11/98; 2/1/99*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *111-126 and 131-142* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *111-126 and 131-142* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *19, 23*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claims 127-130 have been canceled. Claims 111, 114-126, 131-135 have been amended. Claims 136-142 have been added. Claims 111-126 and 131-142 are pending and under examination.

2. The text of those sections of Title 35, U.S.C. Code not included in this Office action can be found in a prior Office Action.

3. The following Office Action contains some NEW GROUNDS of rejection.

Compliance with the Sequence Requirements

4. This application is now in Compliance With Requirements For Patent Applications Containing Nucleotide And/or Amino Acid Sequence Disclosures.

Information Disclosure Statement

5. The Information Disclosure Statement submitted 5/19/98 has been replaced by the Information Disclosure Statement filed 7/28/98. The Information Disclosure Statement filed 5/19/98 was incomplete by not citing the full reference information for each reference. The references cited on the Information Disclosure Statement filed 7/28/98 have been considered.

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, including the method of making the humanized immunoglobulins.

7. The amendment to the first line of the specification to include the status of all parent applications has been noted. The section is incomplete because

a. The phrase "USSN 634,278" fails to denote whether this is the 08/634,278 or 07/634,278 application.

b. The sentence fails to clearly point out the relationship of USSN 07/30,252 to the other applications. Is this a divisional, a continuation or a continuation in part of USSN ##/634,278 or of USSN 07/590,274?

8. The assurance on page 18, section 4-7, that a substitute specification will be provided is noted.

9. The following defect in the Oath/declaration has been newly identified.

Oath/Declaration

10. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not clearly state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56 which occurred between the filing date

of the prior application and the national or PCT international filing date of the continuation-in-part application.

The declaration/oath states "see attached" is written under the statement claiming benefit under 35 U.S.C. 120. A page is apparently attached to the Oath/Declaration, which merely recites a list of US Serial numbers and filing dates, standing alone. The attachment is not signed or dated by the inventors and contains no language suggesting that this is the attachment is the one in which the Oath /Declaration refers. The attachment does not contain the 35 U.S.C. 120 language as required. It is suggested that anew oath/declaration be submitted.

Claim Rejections - 35 U.S.C. § 112

11. Claims 114, 118, 120-121, 124-126, 131-135, 137, 142, wherein they depend upon any of the preceding claims stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 114, 118, 120-121, 124-126, 131-135, 137, 142 wherein they depend upon any of the proceeding claims are vague and indefinite for reciting affinities of "10^8 and 10^{10} M^{-1}" without a limitation that the antibodies would not be more the four fold higher affinity that the parent antibody. As written, the claims appear to recite a method of increasing antibody affinity

more than four fold and for taking an low affinity antibody and producing a high affinity humanized antibody.

b. The rejection of Claims 111 and 115 as indefinite for reciting at least 65% identical to the donor immunoglobulin variable chain region framework has been withdrawn in view of the amendment to include the limitation that "at least 70 amino acid residues identical to those in the acceptor human heavy chain variable region framework".

12. The following are NEW GROUNDS of rejection.

13. Claims 111-112, 115, 116, 139-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 111-112, 115, 116, 139-142 are indefinite for reciting at least 65% or 70% identical to the donor immunoglobulin variable chain region framework because it is not clear which algorithm and what parameters are being use to calculate the percent sequence identity.

14. Claims 111-112, 115, 116, 139-142 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanization procedures, does not reasonably provide enablement for humanization that results in a selected variable region framework which is at least 65% or 70% identical to the donor immunoglobulin variable region framework . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. Claims 111-112, 115, 116, 139-142 are so broad as to encompass humanization procedures that results in a selected variable region framework which is at least 65% or 70% identical to the donor immunoglobulin variable region framework The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and a detailed knowledge of the ways in which the protein's structure relates to its function.

c. Sequence identity between two sequences has no common meaning within the art. See George et al; "Current Methods in Sequence Comparison and Analysis", in Macromolecular Sequencing and Synthesis, Selected Methods and Applications, pages 127-149 1988, Alan R. Liss, Inc and Barton et al "Protein Sequence Alignment and Database Scanning" in Protein

Structure Prediction, A Practical Approach, 1996 IRL Press at Oxford University Press, Oxford, UK, pages 31-63). Barton et al teach that the "results of the analysis are entirely dependent on the choice of scoring results" (page 130, col 1-2, bridging paragraph). George et al teach that percent sequence identity is not an objective property of molecules but is a value arrived at by using algorithms (page 130, columns 1-2, bridging paragraph). The scoring of gaps when comparing one nucleic acid sequence to another introduces uncertainty as to the percent of similarity between two sequences and applies equally to comparison of amino acid sequences.

d. The specification lacks specific algorithm and parameters used to determine percent identity. The specification provides insufficient guidance for one skilled in the art to determine the percent sequence identity of two sequences, albeit amino acid or nucleic acid sequences, without undue experimentation. A table or figure exemplifying a sequence alignment and numerical % sequence identity, without more elaboration, does not satisfy the need for explicit instructions in how to interpret the claims, because it is not possible to work backwards from the example to derive the algorithm and parameters used without undue experimentation.

e. The specification has not enabled determining which sequences are 65 % or 70% identical in view of the lack of guidance concerning algorithms and parameters, as evidenced by Barton et al and George et al. The specification has provided insufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without

sufficient guidance, determination of which variable framework to use is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

15. Claims 114, 118, 120-121, 123, 124-125 and claims 126, 131 132-137, 142 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the previous Office Action as evidenced by Groves et al (Hybridoma, Vol 6(1) 71 1987), Jones et al, (Nature Vol 321 522-525 1986) and Reichmann et al, (Nature Vol 332, 325-327 1988).

a. The response set forth on page 19-21 and the references of Co et al (1992), Caron et al (1992) and Caron et al (WO96/05229 1992) have been considered carefully but are deemed not to be persuasive. The response argues that humanized antibodies made in accordance to the present invention have been shown to have affinities much stronger that their donor immunoglobulin. The claims read upon antibodies which have much stronger affinities, however, the specification and the references used to support the arguments do not show "much higher affinities", but rather much smaller increases in affinities (only 3-8 fold higher). The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

16. The rejection of Claims 114, 118, 122, 123, 125-126 and claims 131-135 wherein they depend upon claims 122, 123, 125-126 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn in view of the amendment to the claims.

17. It is noted that US application 07/290,975 (page 8, lines 3-7) provides support for the limitation "10^8 and 10^{10} M^{-1}" found in claims 114, 118, 13, 120 and 121 and claims that depend upon these. Thus these claims are entitled to the effective filing date of 2/13/89.

Claim Rejections - 35 U.S.C. § 102

18. Claims 111 and 115 stand rejected under 35 U.S.C. 102(b) as being anticipated by Reichmann et al (Nature, Vol 332, 325-327 1988), as evidenced by Cheetham (Prot Engineering Vol 2(3) 170-172, 1988, reference AM in Paper no 10).

a. The response set forth on pages 26-27 has been considered carefully but is deemed not to be persuasive. The response argues that Reichmann et al's changes at position 27 and 30 fall within the Chothia CDR H1 and that this is contrary to the rejected claim. The fact remains that claims 111 and 115 do not contain the argued limitation. Applicant is reminded that the claims define the subject matter of his invention and that the specification cannot be relied upon to

read limitations into the claims. Arguments presented that rely on particular distinguishing features are not persuasive where those features are not recited in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed Cir 1993). Amending the claims to include the argued limitation would obviate this rejection.

Claim Rejections - 35 U.S.C. § 103

19. The rejection of Claims 114, 118, 122-123, 126, and claims 132-135 that depend upon any of these claims under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Reichmann et al (Nature, Vol 332, 325-327 1988), as evidenced by Cheetham (Prot Engineering Vol 2(3) 170-172, 1988, reference AM in Paper no 10) is withdrawn in view of the amendment to the claims.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 111-112, 115-116, 139-142 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over independent claims 1 and 35 of U. S. Patent No 5,693,761 or independent claim 1 of US Patent No 5,530,101 or independent claims 1, 11, 14 and 16 of US Patent No 5,693,762. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims recite the same patent features of humanized antibodies, DNA encoding humanized antibodies and methods of making humanized antibodies wherein the sequence of the heavy or light chain variable region framework is at least 65% identical to the sequence of the donor immunoglobulin heavy or light chain variable region framework.

22. Claims 112 and 113 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,693,761, claim 3 of US patent 5,530,101 and claims 3 and 7 of US patent No 5,693,762. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims recite the same patent features of binding antigen with an affinity constant of at least 10^7 and having no greater than four fold affinity of that of the donor immunoglobulin.

23. Claims 113-114, 117-123, 124-126, 131-138 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10, 11 and 37 of

U.S. Patent No. 5,693,761 and claims 1-4 of US patent 5,585,089. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims recite the same patent feature of wherein each of the donor amino acids are adjacent to a CDR in the donor immunoglobulin sequence, are capable of interacting with amino acids in the CDRs or is typical at its position for human immunoglobulin sequences and the substituted amino acid in the acceptor is rare at its position for the human immunoglobulin sequences.

24. As set forth in the previous Office Action, the declaration to correct the inventorship under 37 C.F.R. 1.48 (b) (paper no 4 filed 3/96) has been considered carefully and is deemed to be sufficient. Accordingly, the names Schneider, Landolfi, Coelingh and Selick will be deleted.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

26. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie E. Reeves, Ph.D.

(703) 308-7553

JULIE REEVES
PATENT EXAMINER

John J. Doll, Director
Technology Center 1600